REMARKS

Claims 1-4, 6-17, 19-37 remain under active prosecution in the present application. Claims 5 and 18 have been canceled. Applicant respectfully asserts that all amendments are supported by the original disclosure and do not introduce new matter. Moreover, Applicants further respectfully assert that the amendments merely clarify the scope of the claims.

The invention will first be briefly reviewed. The present invention is a transgenic aquatic organism that can be used to determine the levels of environmental contaminants in aquatic samples. The organism contains a transgene that is comprised of a pollution-inducible response element and a reporter gene. The response element is selected based on the contaminant that is desired to be measured, for example, dioxin or mercury. In one embodiment of the present invention, the reporter gene encodes a bioluminescent molecule. The reporter gene is activated when the organism is in the presence of contaminants specific to the response element, and the resulting activity of the reporter gene can be easily measured, allowing for ready determination of environmental pollution. The organism can then be de-contaminated and re-used

Claim Rejections – 35 U.S.C. § 112 – 1st paragraph

In the subject Office Action dated May 26, 2005, the Examiner has rejected claims 1-37 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner contends that the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner has expressed concern that claims 1 and 2 recite a transgenic organism, defined by the specification as an organism that contains "one or more transgenes within its genome." The Examiner rejected the claims, asserting that no transgenic fish were demonstrated to contain transgenes that were responsive to contaminants, thereby failing to overcome the unpredictability set forth with respect to transgene expression. However, Applicant's respectfully assert that the claims comply with 35 U.S.C. § 112 for the following reasons.

First, in the interview with the Examiner on November 3, 2005, it was established that the USPTO routinely accepts a broader definition of the term "transgenic" such that a transient incorporation of a transgene would satisfy the term transgenic. In fact, it was stated by the examiner that for a claim to be limited to a stably incorporated gene, the term "stable" must be used. In light of this, the term transgenic as used is broad enough to fully describe the claimed invention, regardless of whether the transgene is "stably" integrated or not.

Second, the lack of transgene transmission to offspring is inconsequential to a determination of whether the transgene is stably incorporated or not in the claimed invention. In fact, in this case, a stably transfected organism appears much like one would expect a transiently transfected organism to appear, in that there is no expression in the F1 and F2 generations. In the case of zebrafish, the transgene in the F0 generation is either silenced or excised in the F1 or F2 generation, creating the appearance of a transient incorporation in the F0 organism. As a result, the lack of expression in offspring is not sufficient to conclusively determine whether a particular transgenic animal is stably or transiently transfected. As such, describing the organism as transgenic, even if limited to stable transgenics (per reference to the specification), does not render the present invention not enabled.

Finally, the type of transgene incorporation (whether transient or stable) is not essential to the present invention. Whether stably integrated or merely transiently expressed in the organism, all that need be known is that the transgene is expressed, and to what extent, as a single organism may be assessed for gene expression, standardized, then used repeatedly. As long as each transgenic organism is standardized against a reference containing a known amount of contaminant, verifying the existence and expression of the transgene, the invention is fully operable. As the fish can be de-toxified and used repeatedly, stable integration allowing passage of the transgene to offspring is unnecessary and unrelated to the invention.

The Examiner has also rejected claims 1 and 2 on the basis that the term "known standard" is not enabling. Claims 1 and 2 have been amended to more clearly state the method that must be used to practice the invention. The Examiner has expressed concern that the claims may be deficient because they do not require a determination of background expression for each organism prior to use. (Office Action, p. 4, lines 1-3.)

The specification must be enabling at the time the application was filed. However, everything necessary to practice the invention need not be disclosed. If something is well known to one skilled in the art, it may be omitted. *In re Buchner*, 929 F. 2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991).

In making the determination of enablement, the examiner shall consider the original disclosure and all evidence in the record, weighing evidence that supports enablement against the evidence that the specification is not enabling. In the mid-1800's the Supreme Court reasoned that a specification would be defective if it required one with skill to "experiment" in order practice the claimed invention. *Wood v. Under Hill,* 46 U.S. (4 How.) 1 (1847). The standard for determining whether the specification met the enablement requirement was recast in the later Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in art can make and use the invention without undue experimentation. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

1. the breadth of the chemical patent claims,
2. the nature of the invention,
3. the state of the prior art,
4. the level of one of ordinary skill,
5. the level of predictability in the art,
6. the amount of direction provided by the inventor,
7. the existence of working examples, and

8. the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that chemical patent claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement).

In *Wands*, the court noted that the there was no disagreement as to the facts, but merely a disagreement as to the interpretation of the data and the conclusion to be made from the facts. *In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1403-07. The court held that the specification was enabling with respect to the chemical patent claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the chemical patent application was filed;" and "all of the methods needed to practice the invention were well known." Id. at 740, 8 USPQ2d at 1406. After considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." Id., 8 USPQ2d at 1407.

I t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole. Id. at 737 & 740, 8 USPQ2d at 1404 & 1407. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the chemical patent application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d at 1562, 27 USPQ2d at 1513. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404.

Therefore, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986),

cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of experimentation are known and contemplated, 35 U.S.C. Section 112, is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); and *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643(CCPA 1965); see also *In re Brana,* 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993). It is not necessary to specify the method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of assays having similar physical or biological activity, would be able to discern an appropriate steps for method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. Section 112.

Claims 1 and 2 have now been amended to address the Examiner's concerns. Claims 1 and 2 now require the steps of: introducing into an aquatic organism a DNA construct (containing the necessary elements), exposing the transgenic organism to a water sample to be tested, detecting reporter gene expression, and *correlating* the detected expression <u>of the transgenic organism</u> to <u>a *reference standard* comprising an aquatic source containing a known contaminant concentration</u> thereby determining the quantity of contaminants in the water sample. The underlined portions represent amendments made to claims 1 and 2 and find full support in the specification. (See paragraph 59.)

The presently amended claims 1 and 2 render the present invention fully enabled for the following reasons. First, the amendments clarify the standard used. While it is Applicant's position that a "known standard" is readily known in the art in light of the specification and the state of the art at the time the application was submitted, the present amendments further clarify the method and the standard used to determine contaminant concentrations. Specifically, the claims now require that the *expression of the transgenic organism* be *correlated to a reference standard* that consists of an aquatic source *containing a known contaminant concentration.* Claims 1 and 2 now clearly describe the method step in the invention such that one skilled in the art could make and use the invention claimed.

While Applicant respectfully maintains that correlating expression to a "known standard" is intuitive in the art, these amendments make clear that a standard water sample containing a *known level of contaminant* must be used as a *reference* to standardize the transgenic organism. It is well understood by one skilled in the art that any transgenic organism will have variable expression, and any variable *must necessarily be normalized* before using an organism to measure or predict an outcome. The fact that this is an assumed and well known step in the method is evidenced in the specification at paragraphs 84 and 59. At paragraph 84, a dose-dependent curve demonstrating transgene responsiveness to known concentrations is described. A dose-dependent curve such as this is one means by which a reference standard can be created to allow for accurate measurement of contaminant concentrations in aquatic samples. Paragraph 59 cites use of a reference standard such as that claimed in the present invention. This concept of standardizing results is well recognized in the art, as there is no reliability of experimental results unless intervening variables are normalized. The amended claims 1 and 2 now define the steps of standardization with clarity, rendering the present invention enabled under 35 U.S.C. § 112.

Claim Rejections – 35 U.S.C. § 112 – 2nd paragraph

The Examiner has rejected claims 18-34 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner contends that claim 18 is unclear because it contains abbreviated gene names. Applicant has canceled claim 18. The rejection, therefore, no longer applies. Claims dependant on claim 18 have been amended so that they are now dependant on claim 4.

CONCLUSION

In light of the amendments and remarks made herein, it is respectfully submitted that the claims currently pending in the present application are in form for allowance. Accordingly, reconsideration of those claims, as amended herein, is earnestly solicited. Applicants encourage

the Examiner to contact their representative, Stephen R. Albainy-Jenei at (513) 651-6839 or salbainyjenei@fbtlaw.com.

The Commissioner for Patents is hereby authorized to charge any deficiency or credit any overpayment of fees to Frost Brown Todd LLC Deposit Account No. 06-2226.

Respectfully submitted,

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